

RECEIVED

U.S.S.N. 09/360,242
MCDONALD *et al.*
AMENDMENT

—66. The method of claim 29, wherein the chemokine targeting agent is a chemokine that is a member of the superfamily of chemokines that interact with at least one of the chemokine receptors selected from the group consisting of the CC-, CXC-, CX3C- and XC-receptors.—

—67. The method of claim 29, wherein the chemokine targeting agent is a chemokine that is a member of the superfamily of chemokines that interact with at least one of the chemokine receptors selected from the group consisting of the CC- and CXC- receptors.—

62 —68. The method of claim 65, wherein the chemokine is selected from the group consisting of IL-8, GCP-2, GRO- α , GRO- β , GRP- γ , ENA-78, PBP, CTAP III, NAP-2, LAPF-4, MIG, PF4, IP-10, SDF-1 α , SDF-1 β , SDF-2, MCP-1, MCP-2, MCP-3, MCP-4, MCP-5, MIP-1 α , MIP-1 β , MIP-1 γ , MIP-2, MIP-2 α , MIP-3 α , MIP-3 β , MIP-4, MIP-5, MDC, HCC-1, LD78 β , eotaxin-1, eotaxin-2, I-309, SCYA17, TARC, RANTES, DC-CK-1, lymphotactin, and fractalkine.—

—69. The method of claim 65, wherein the chemokine is selected from the group consisting of lungkine, ALP, Tim-1, chemokine α -5, chemokine α -6 and chemokine β 15.—

—70. The method of claim 29, wherein the chemokine receptor selected from the group consisting of CXCR-1, CXCR-2, CXCR-3, CXCR-4, CXCR-5, CCR-1, CCR-2A, CCR-2B, CCR-3, CCR-4, CCR-5, CCR-6, CCR-7, CCR-8, CCR-8, CX3CR-1, XCR1, Duffy antigen receptor for chemokines (DARC) and CD97.

—71. The method of claim 65, wherein the chemokine receptor is selected from the group consisting of DARC, CXCR-1, CXCR-2, CXCR-3, CXCR-4, CCR-1, CCR-2A, CCR-2B, CCR-3, CCR-4, CCR-5, CCR-6, CCR-7, CCR-8, CX3CR-1, and CD97.—

U.S.S.N. 09/360,242
MCDONALD *et al.*
AMENDMENT

1.44
-74
-72. A method for inhibiting activation, proliferation or migration of immune cells, comprising contacting immune cells with a conjugate that comprises a targeted agent and a chemokine receptor targeting agent or portion thereof, whereby activation, proliferation, migration or the immune cells is inhibited, wherein:

the targeted agent or portion thereof is a toxin;

the chemokine receptor targeting agent is a chemokine or a fragment of thereof that binds to a chemokine receptor and internalizes the targeted agent; and

the conjugate binds to a chemokine receptor resulting in internalization of the targeted agent in cells bearing the receptor. —

73
-73. The method of claim 72, wherein the conjugate comprises the following components: (chemokine receptor targeting agent)_n, (L)_q and (targeted agent)_m, wherein:

L is a linker for linking the chemokine or fragment thereof to a targeted agent;

m and n, which are selected independently, are at least 1; and

q is 0 or more as long as the resulting conjugate binds to the targeted receptor, is internalized and delivers the targeted agent;

the resulting conjugate binds to a receptor that interacts with and internalizes a chemokine, whereby the targeted agent(s) is internalized in a cell bearing the receptor; and

when the conjugate contains a plurality of targeted agents, the targeted agents are the same or different, and when the conjugate contains a plurality of chemokine receptor targeting agents, the targeting agents are the same or different. —

-74. The method of claim 73, wherein m and n, which are selected independently, are 1-6. —

-75. The method of claim 73, wherein q is 1, n is 2 and m is 1. —

U.S.S.N. 09/360,242
MCDONALD *et al.*
AMENDMENT

—76. The method of claim 73, wherein the chemokine specifically binds to chemokine receptors on activated leukocytes.—

—77. The method of claim 73, wherein the chemokine specifically binds to chemokine receptors on activated cells selected from mononuclear phagocytes (MNP), leukocytes, natural killer cells, dendritic cells, T lymphocytes and B lymphocytes.—

—78. The method of claim 76, wherein the activated leukocytes are selected from basophils, neutrophils, eosinophils or combinations of any two or more thereof.—

1.2
—79. The method of claim 73, wherein the chemokine is a member of the superfamily of chemokines that interact with at least one of the chemokine receptors selected from the group consisting of the CC-, CXC-, CX3C- and XC-receptors.—

—80. The method of claim 73, wherein the chemokine is a chemokine that is a member of the superfamily of chemokines that interact with at least one of the chemokine receptors selected from the group consisting of the CC- and CXC- receptors.—

2.4 E3
—81. The method of claim 65, wherein the chemokine is selected from the group consisting of IL-8, GCP-2, GRO- α , GRO- β , GRP- γ , ENA-78, PBP, CTAP III, NAP-2, LAPF-4, MIG, PF4, IP-10, SDF-1 α , SDF-1 β , SDF-2, MCP-1, MCP-2, MCP-3, MCP-4, MCP-5, MIP-1 α , MIP-1 β , MIP-1 γ , MIP-2, MIP-2 α , MIP-3 α , MIP-3 β , MIP-4, MIP-5, MDC, HCC-1, LD78 β , eotaxin-1, eotaxin-2, I-309, SCYA17, TARC, RANTES, DC-CK-1, lymphotactin, and fractalkine.—

—82. The method of claim 40, wherein the targeted agent, when internalized in a cell, alters metabolism or gene expression in the cell, regulates or alters protein synthesis in the cell, inhibits proliferation of the cell or kills the cell.—

—83. The method of claim 29, wherein the targeted agent is selected from among ribosome inactivating proteins (RIPs) and bacteriocins.—

U.S.S.N. 09/360,242
MCDONALD *et al.*
AMENDMENT

—84. The method of claim 73, wherein the toxin is a ribosome inactivating protein or a toxic subunit thereof.—

—85. The method of claim 29, wherein the targeted agent is a toxin that is a ribosome inactivating protein or a toxic subunit thereof.—

86. A method of treating a disease or disorder associated with an inflammatory response, comprising:

identifying immune cells that are activated in the disease or disorder;

identifying chemokine receptors expressed on the cells;

preparing a conjugate or plurality thereof containing toxin linked to a chemokine or a plurality of chemokines that specifically bind to the identified chemokine receptors and effect or facilitate internalization of the toxin into the cells; and

contacting the immune cells with the conjugate or plurality thereof.—

—87. The method of claim 86, wherein a plurality of conjugates that bind to a plurality of chemokine receptors are prepared, and the immune cells are contacted with each of the conjugates simultaneously or sequentially.—

Please amend claims 26-29, 31, 36, 38, 40, 42, 44, 48, 49, 51-53 and 57 as follows:

26. The method of claim [25] 29, wherein the immune effector cells are leukocytes that express chemokine receptors.

27. The method of claim [25] 29, wherein the inflammatory response results in secondary tissue damage.

28. The method of claim [25] 29, wherein the immune effector cells are selected from mononuclear phagocytes (MNP), leukocytes, natural killer cells, dendritic cells, T lymphocytes and B lymphocytes.

29. (Amended) A method for treating pathological conditions associated with inflammatory responses and secondary tissue damage associated with activation, proliferation and migration of immune effector cells

U.S.S.N. 09/360,242
MCDONALD *et al.*
AMENDMENT

by inhibiting activation, proliferation or migration of immune effector cells, comprising administering a conjugate to an animal[mammal], whereby [an inflammatory response associated with] activation, proliferation, migration or the immune effector cells is inhibited, thereby inhibiting the inflammatory response, wherein:

the conjugate comprises a targeted agent and a chemokine receptor targeting agent or a portion thereof[, wherein];

the chemokine receptor targeting agent is a chemokine, an antibody that specifically binds to a chemokine receptor or a fragment of the chemokine or antibody, wherein the chemokine, antibody or fragment thereof binds to the receptor and internalizes the targeted agent in a cell;

the targeted agent or portion thereof, when internalized in a cell, alters metabolism or gene expression in the cell, regulates or alters protein synthesis in the cell, inhibits proliferation of the cell or kills the cell; and

the conjugate binds to a chemokine receptor resulting in internalization of the targeted agent in cells bearing the receptor.

31. (Amended) The method of claims 29, wherein the disorder or disease state is selected from the group consisting of CNS injury, CNS inflammatory diseases, neurodegenerative disorders, heart disease, inflammatory eye diseases, inflammatory bowel diseases, inflammatory joint diseases, inflammatory kidney or renal diseases, inflammatory lung diseases, inflammatory nasal diseases, inflammatory thyroid diseases, inflammatory responses associated with bacterial or viral infections and cytokine-regulated cancers.

36. (Amended) The method of claim 35, wherein the immune effector cells are activated leukocytes.

38. (Amended) A method of inhibiting proliferation, migration or activation of cells bearing chemokine receptors, comprising contacting the cells with an effective amount of a conjugate that comprises a targeted agent and a chemokine receptor targeting agent, or a portion thereof, wherein the conjugate

U.S.S.N. 09/360,242
MCDONALD *et al.*
AMENDMENT

binds to a chemokine receptor resulting in internalization of the targeted agent in cells bearing the receptor.

40. (Amended) A method for treating secondary tissue damage and associated disease states, comprising administering to a subject in need thereof an effective amount of a therapeutic agent that inhibits the proliferation, migration or physiological activity of secondary tissue damage-promoting inflammatory cells, wherein the therapeutic agent is a conjugate that comprises a chemokine receptor targeting agent and a targeted agent or portion thereof selected so that conjugate binds to a chemokine receptor and internalizes the targeted agent, which inhibits the proliferation, migration or physiological activity of the secondary tissue damage-promoting cells.

42. (Amended) The [A] method of claim [25] 29, wherein the conjugate is selected from the group consisting of OPL98104, OPL98112, OPL98108, OPL98102, OPL98110, OPL98106, OPL98101, OPL98109, OPL98105, OPL98103, OPL98111 and OPL98107.

44. (Amended) The method of claim [43] 29, wherein the conjugate comprises the following components: (chemokine receptor targeting agent)_n, (L)_q and (targeted agent)_m, wherein:

L is a linker for linking the chemokine receptor targeting agent to a targeted agent;

chemokine receptor targeting agent is any moiety that selectively binds to a chemokine receptor and effects internalization of the conjugate;

m and n, which are selected independently, are at least 1; and

q is 0 or more as long as the resulting conjugate binds to the targeted receptor, is internalized and delivers the targeted agent;

the resulting conjugate binds to a receptor that interacts with and internalizes a chemokine, whereby the targeted agent(s) is internalized in a cell bearing the receptor; and

U.S.S.N. 09/360,242
MCDONALD *et al.*
AMENDMENT

when the conjugate contains a plurality of targeted agents, the targeted agents are the same or different, and when the conjugate contains a plurality of chemokine receptor targeting agents, the targeting agents are the same or different.

48. (Amended) The method of claim [43] 44, wherein the chemokine receptor targeting agent specifically binds to chemokine receptors on activated leukocytes.

49. (Amended) The method of claim [43] 44, wherein the chemokine receptor targeting agent specifically binds to chemokine receptors on activated cells selected from mononuclear phagocytes (MNP), leukocytes, natural killer cells, dendritic cells, T lymphocytes and B lymphocytes.

50. (Amended) The method of claim 49, wherein the activated leukocytes are selected from basophils, neutrophils, eosinophils[, and] or combinations of any two or more thereof.

51. (Amended) The method of claim [43] 44, wherein the targeted agent is a toxin, a nucleic acid or a therapeutic protein.

52. (Amended) The method of claim [43] 44, wherein the chemokine receptor targeting agent and targeted agent are linked directly via a covalent or ionic linkage.

53. (Amended) The method of claim [43] 44, wherein the chemokine receptor targeting agent and [targeting] targeted agent are joined via a linker.

57. (Amended) The method of claim [55] 44, wherein the chemokine receptor targeting agent is a chemokine[, an antibody that specifically binds to a chemokine receptor] or a fragment thereof[of the chemokine or antibody, wherein the fragment] that binds to the receptor and internalizes the targeted agent.